

### REMARKS

The amendments and remarks presented herein place the claims in condition for allowance. Applicant respectfully requests reconsideration in view of these amendments and arguments.

#### Interview

Applicant thanks Examiner Souw for his participation and assistance during the February 7, 2005 personal interview and his consideration of applicant's arguments.

As noted in the Interview Summary Record and discussed in more detail below, various stated differences between applicant's method and the prior art of record were discussed.

#### Amendments to the Claims

Applicant has amended claim 1 to more particularly point out and distinctly claim his invention. None of these amendments introduces new matter. They are fully supported by the specification and the claims, as originally filed. Applicant requests their entry.

In particular, applicant has amended claim 1 to clarify that the analyte is irradiated at a mid-IR wavelength that is offset from the IR absorption maximum of the energy

absorbing molecules that are admixed with the analyte. Amended claim 1 also clarifies that irradiation of the analyte at this offset mid-IR wavelength produces analyte gas phase ions, wherein a preponderance of the ions for at least one given mass has higher order charge states. Applicant has also amended the claim to move the former preamble language regarding the preponderance of higher order charge states to the main body of the claim. Neither amendment narrows the scope of the original claim. They merely clarify the characteristics of the mid-IR wavelength recited in the original claim.

Applicant has also amended claims 3, 7, 9-11, 13-18, 20, and 23-28 to correspond them to amended claim 1. None of these amendments introduces new matter or narrows the scope of the original claims. They are fully supported by the specification and claims as originally filed. Applicant requests their entry.

#### Rejections Under 35 U.S.C. § 103(a)

Claims 1, 2, 4, 7-10, 12-25 and 28 stand rejected under 35 U.S.C. § 103(a) over Hillenkamp, U.S. Patent 6,706,530 ("Hillenkamp") in view of Odom et al., U.S. Patent 6,451,616 ("Odom") and Gauthier et al., *Anal. Chimica Acta*, Vol. 246, pp 211-225, 1991 ("Gauthier"). Claims 3 and 21-23 stand rejected under § 103(a) over Hillenkamp in view of Odom and Gauthier and in further view of Peters et al., U.S. patent application 20030228700. Claims 5 and 6 stand rejected under § 103(a) over Hillenkamp in view of Odom and Gauthier and in further view of

Doroshenko et al., U.S. Patent 6,683,300. Claim 11 stands rejected under § 103(a) over Hillenkamp in view of Odom and Gauthier and in further view of Hofstadler et al., U.S. Patent 6,342,393. Claims 26 and 27 stand rejected under § 103(a) over Hillenkamp in view of Odom and Gauthier and in further view of Crooke et al., U.S. Patent 6,656,690. Applicant traverses these rejections.

Applicant's claimed invention is directed to a method for laser desorption ionization of an analyte in the presence of energy absorbing molecules. As explained in the specification and recited in all of the claims, ionization results from irradiation of the analyte at a mid-IR wavelength. This mid-IR wavelength has two requirements: the wavelength is offset from the IR absorption maximum of the energy absorbing molecules, and irradiation of the analyte at this wavelength results in the production of analyte gas phase ions in which a preponderance of the ions for at least one given mass has higher order charge states. For example, as described in FIG. 3 and at page 29, line 26 to page 30, line 9, irradiation of a sample with an offset mid-IR wavelength yields ions in which a preponderance have the higher order +2 and +3 charge states versus ions having the +1 charge state.

The Examiner contends that Hillenkamp "discloses a method for producing a preponderance of gas phase ion having higher order charge states." The Examiner concedes that Hillenkamp does "not expressly recite[]" the use of a mid-IR wavelength that is offset from the IR absorption maximum of the energy absorbing molecules. However, he nevertheless contends that such a feature is "inherently comprised" in Hillenkamp.

The Examiner further contends that Odom discloses a laser desorption using an IR laser wavelength that is "offset from an IR absorption maximum of the energy absorbing molecules." Finally, the Examiner contends that Gauthier describes "off-resonance dissociation and fragmentation of molecules." (Office Action at page 3.)

The Examiner, therefore, concludes that it would have been obvious to use Hillenkamp's ionization method with the offset mid-IR wavelength allegedly suggested by Odom and Gauthier. As supposed motivation for such a combination, the Examiner states that "there are plenty of laser types that can be used for such off-resonance processes, such that the choice of laser type is not critical, and hence, the MALDI process is much more easier to implement." (*Id.* at page 3; emphasis added.)

Applicant disagrees with the Examiner's assertions and conclusions for at least the following six reasons.

1) Although Hillenkamp refers to multiply charged ions and some advantages thereof in MALDI-MS, it provides no teaching or suggestion as to how a preponderance of ions having a higher charge state could be produced.

2) Even assuming that Hillenkamp would have motivated the skilled worker to enhance the production of multiply charged ions, it provides no teaching, suggestion, or motivation that it is the combination of the offset IR wavelength and the IR absorption maximum of the energy absorbing molecules that is important or that it would ever be

useful in producing highly charged ions. In contrast, Hillenkamp teaches away from these parameters by disclosing other, unrelated parameters as possible variables for further optimization. These include the spot size of the laser, the duration of irradiation, and the analyte-to-matrix ratio. Hillenkamp column 16, lines 50-53:

In IR-MALDI there is also a pronounced dependence on the A/M [analyte-to-matrix] ratio of the yield of (non-specific) analyte oligomers or multiply charged ions. These tendencies are more pronounced in IR- as compared to UV-MALDI.

(See also *Id.* at column 7, lines 55-57.)

3) Because Hillenkamp fails to provide any teaching, suggestion, or motivation of using an offset mid-IR wavelength, and instead teaches away, by its silence, from using such an IR wavelength, there would have been no motivation to combine Hillenkamp with the disclosures of either Odom or Gauthier.

4) Neither Odom nor Gauthier provide any teaching or suggestion that would remedy Hillenkamp's failure to teach or to suggest the use of an offset mid-IR wavelength to enhance the production of higher order charged ions.

5) Any motivation to combine Hillenkamp with Odom is lacking for at least another reason: Hillenkamp and Odom are each directed to two different methods. Hillenkamp refers to the use of a matrix material that absorbs laser energy and, thereby, facilitates the desorption and ionization of analytes in intimate contact therewith on the surface of a probe. In

contrast, Odom refers to a system in which analytes are "bound or bonded to solid surfaces." (Odom at column 2, lines 50-51; emphasis added.) Odom's laser irradiation effects "selective cleavage of a bond in an absorbate/substrate system." (*Id.* at Abstract.) Thus, Odom's reference to an "off-resonance" laser frequency, as quoted by the Examiner, relates to this the frequency absorbed by the covalent bond during photolytic cleavage. (*Id.* at column 7, lines 1-10.) In contrast, in Hillenkamp's IR-MALDI methods the matrix material adsorbs laser energy at a particular frequency. The laser energy is not used to cleave covalent cleaving bonds or otherwise fragment the molecule. ("The lower degree of fragmentation gives IR-MALDI an advantage over UV-MALDI," Hillenkamp at column 18, lines 59-60.) Hence, the bond cleavage methods of Odom would have been contrary to the stated purposes of Hillenkamp, and, therefore, a skilled worker would not have been motivated to combine them.

6) There would also have been no motivation to combine Hillenkamp with Gauthier. Gauthier's use of the term "off-resonance," relied upon by the Examiner, is completely different than the meaning of "offset" in applicant's claimed invention. In the present invention, "offset" refers to the difference between the irradiating mid-IR wavelength and the IR absorption maximum of the energy absorbing molecules during laser desorption/ionization. In contrast, and as clearly stated in Gauthier's Abstract, the term "off-resonance" refers to a "sustained ( $\geq 500$  ms) off-resonance electric field pulse," which is used for translationally exciting an ion for collision-activated fragmentation. (Gauthier at Abstract, emphasis added.) In other words, it refers to the frequency of


the electronics of the system, not to the frequency of the laser. Therefore, Gauthier's "off-resonance electric field pulse" is applied to translationally excite the ion after desorption/ionization. The steps of desorption/ionization and translational excitation are separate and distinct. Accordingly, there would have been no reason or motivation to combine these respective documents.

Therefore, for at least any one of the above reasons, Hillenkamp, Odom, and Gauthier, either alone or in combination, do not teach, suggest, or motivate the skilled worker to practice a method having all of the elements of applicants' amended claim 1. Moreover, Hillenkamp, Odom, and Gauthier, either alone or in combination, do not teach, suggest, or motivate the skilled worker to practice a method having all of the elements of claims 2-28, which all depend from claim 1. Accordingly, applicant respectfully requests that the Examiner reconsider and withdraw these rejections.

CONCLUSION

Applicant respectfully submits that all of the pending claims are in form for allowance. If the Examiner believes, however, that any matters remain outstanding, applicant requests that the Examiner call the undersigned.

Respectfully submitted,

  
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